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Improved results after lung transplantation – analysis of factors

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Summary

Better recipient selection, sophisticated postoperative surveillance and new immunosuppressive and anti-infective regimens can improve the results of lung transplantation.

We compared the results of lung transplants performed between 1992 and 1996 (early period; 47) and between 1997 and 2000 (recent period; 46) in a cohort study to assess which factors influenced survival. Estimates of relative hazards were adjusted for possible confounding effects with the use of Cox regression analysis.

Overall 2-year survival was 70%. Survival by this time was significantly better in the recent period (82% vs. 60%; p = 0.0093). Acute rejection episodes and death due to BOS were less frequent in the recent period. There were no technical failures, and the cumulative incidence of BOS was low (34% at 5 years). The beneficial effect of the transplantation date 1997 or later at a hazard ratio of 0.33 (95% CI, 0.13–0.84) was materially changed only by the adjustment for ganciclovir prophylaxis (0.50; 95% CI, 0.09–2.91) and immunosuppression with mycophenolate mofetil (0.80; 95% CI, 0.27–2.36). After adjustment for both ganciclovir and mycophenolate mofetil, the beneficial time period effect was completely removed (1.24; 95% CI, 0.14–11.39).

Immunosuppressive therapy with mycophenolate mofetil and use of ganciclovir prophylaxis in addition to careful postoperative surveillance and surgical expertise can lead to improved results after lung transplantation.

Keywords: lung transplantation; transbronchial biopsy; acute rejection; cytomegalovirus; immunosuppression; mycophenolate mofetil; ganciclovir; bronchiolitis obliterans

Introduction

During the past two decades, lung transplantation has become a successful therapy for end-stage diseases of the lungs and the pulmonary circulation [1, 2]. According to the registry of the International Society for Heart and Lung Transplantation, two- and five-year survival rates of 65% and 47%, respectively, can be achieved [3]. This success results from careful selection of patients, improved surgical techniques, organ preservation and sophisticated postoperative management. However, the main obstacle to long-term success of lung transplantation remains chronic rejection occurring in up to two thirds of the patients [4, 5]. It is characterised histologically by bronchiolitis obliterans and a variable degree of pulmonary vascular involvement. The clinical hallmark is a progressive fall in forced expiratory volume in one second accompanied by increasing dyspnoea on exertion. The term "bronchiolitis obliterans syndrome" (BOS) has been created to denote allograft deterioration secondary to progressive airway disease for which no other cause is detectable [6].

The value of enhanced immunosuppressive therapy in patients with BOS remains unknown, and at least one third of the patients will progress to end-stage respiratory failure. The most important risk factors for the development of BOS are the number of previous acute rejection episodes, the occurrence of persistent rejection after treatment of acute rejection episodes and possibly cytomegalovirus infection [7–11].

The role of transbronchial lung biopsy in the diagnosis of acute rejection in symptomatic patients was established during the first decade of clinical lung transplantation [12]. In 1992, Trulock et al. reported an unexpectedly high rate of signif-

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icant acute rejection episodes in biopsies performed for surveillance in clinically stable lung transplant recipients [13]. Thus, based on this experience and hypothesising that early detection and treatment of asymptomatic acute rejection might reduce the subsequent occurrence of BOS, we adopted a strict regimen of monthly surveillance biopsies for the first six months and subsequently confirmed the findings of Trulock [14]. Hence, in the search for new treatment strategies we were among the first to use mycophenolate mofetil for patients with recurrent acute rejection episodes and BOS [15], and also as part of the primary maintenance immunosuppressive regimen.

Moreover, shortly after the introduction of oral ganciclovir we started an open trial of prolonged prophylaxis which resulted in a reduced incidence of cytomegalovirus disease and BOS [16].

As reflected by the registry data many centers have experienced better survival of patients transplanted during recent years [3], and a multitude of aspects might have contributed to this improvement. Hence, we were interested in the most important factors affecting survival analysing the data of our programme with special regard to new immunosuppressive and antiviral strategies.

Methods

Patients

Between November 1992 and April 2000 lung transplant surgery was performed in 93 patients. One patient underwent a repeated transplant after 21 months because of BOS and was considered as a single case completed at the time of retransplantation.

All patient data, transplantation variables, immunosuppressive and anti-infective treatments, complications and outcome variables were retrospectively analysed comparing the time period from November 1992 until December 1996 (early period) and from January 1997 until April 2000 (recent period).

Surgery and clinical management

All operative procedures were performed by a single surgeon (W.W.) using standardised techniques [17–19], which were modified as follows [20]: the bronchus anastomosis was performed first using running 4-0 polydioxanone sutures on the membranous portion and interrupted sutures on the cartilaginous portion. The anastomosis was covered with peribronchial tissue from the recipient. Thereafter, the atrial and arterial anastomosis were done with running sutures using 4-0 and 5-0 prolene. Except in the last three donor lungs in which low-potassium-dextran was used, the lungs were flushed with prostaglandin E1 and Euro-Collins solution. Permissive intraoperative hypercapnia, high-frequency jet ventilation and continuous intra-arterial blood gas monitoring was used to avoid cardiopulmonary bypass whenever possible. The latter was mainly used in cases with primary or thromboembolic pulmonary hypertension. All transplants were ABO-identical, and none was HLA-matched.

The maintenance immunosuppression consisted of cyclosporine aiming at a monoclonal cyclosporine A trough level of 180–250 µg per liter, azathioprine 2 mg per kg of body weight per day, and prednisone 0.5 mg·per kg of body weight per day, tapered to about 10 mg daily within the first 6 months. Antithymocyte globulin was routinely used as induction immunosuppression, but 7 of the last 13 patients received basiliximab in a randomised fashion instead. In 1995, all patients were converted from regular cyclosporine to neoral. From August 1997 to March 1999, seventeen patients were randomised to receive either azathioprine (8) or mycophenolate mofetil 3 grams per day for three months, and 2 grams per day thereafter (9) in an open, unblinded fashion. Thereafter, mycophenolate mofetil was primarily used in all patients. Acute rejection was treated with prednisone pulses of 0.5 to 1 gram for three days. All patients with recurrent acute rejection episodes or BOS were routinely treated with inhaled fluticasone 1000 µg twice daily and since 1997 with 12 cycles of extracorporeal photochemotherapy [21].

Perioperative antibiotic prophylaxis consisted of ceftriaxone or an anti-pseudomonas combination tailored to the pretransplant bacteriology in cystic fibrosis patients. Treatment was adapted according to detected bacterial strains. All patients received cotrimoxazol three double strength tablets per week. Aspergillus colonisation was treated with oral itraconazole and inhaled amphotericin B. Acute bacterial, viral or fungal infections were treated according to standard criteria.

Routine clinical, laboratory, functional and radiological evaluations were performed daily during the first week, and every 2 to 3 days thereafter. During the second month the evaluations were done weekly, and thereafter at a maximum of six week intervals.

Patients measured their body weight, body temperature and lung function on a daily basis. A sustained decrease in lung function of more than 10% was followed up with extensive clinical investigations.

Bronchoscopic techniques

Monthly surveillance bronchoalveolar lavage and transbronchial biopsy were routinely performed in clinically stable recipients during the first six months, in patients with new symptoms, signs, roentgenographic infiltrates, or declining lung function, and for follow-up one month after a previous pathological finding [14].

Bronchoscopy was performed under topical anaesthesia and intravenous sedation. Three to five biopsies were obtained from each lobe of one lung under fluoroscopic guidance.

Acute rejection was diagnosed by presence of perivascular mononuclear infiltrates. Severity of acute rejection was graded according to criteria of the International Society for Heart and Lung Transplantation [22].

Cytomegalovirus prophylaxis and surveillance

Initially, seropositive patients or recipients of seropositive organs were given acyclovir 2400 mg daily. From May 1994 five patients received intravenous ganciclovir 5 mg·per kg of body weight twice daily until day 21, and once daily thereafter until day 90. Since May 1995, patients at risk received oral ganciclovir 3000 mg daily until the prednisone dose was reduced to less than 15 mg [16]. All seronegative patients receiving a seronegative organ were given acyclovir.

Virological assessments (pp-65 antigen, IgG) were

obtained twice weekly during the first month and on each visit thereafter. Cytomegalovirus disease was defined as histological evidence of cytomegalic inflammation accompanied by positive viral cultures or polymerase chain reaction.

Outcome measures

Within the first two postoperative weeks acute rejection was diagnosed on clinical grounds (new or changing radiographic infiltrates, deterioration of lung function) after the exclusion of infection. Diagnosis was confirmed by resolution of symptoms and signs within 48 hours after administration of pulse steroids and lack of the emergence of other clinical problems potentially responsible for the abnormalities. From the third week all patients with suspected acute rejection underwent lung biopsy as described above. Histologically, acute rejection was considered to be significant and treated accordingly from grade A2 or higher.

BOS was defined according to the International Society for Heart and Lung Transplantation [6] based on the percentage of forced expiratory volume in one second compared to the average of the best two baseline values after transplantation: grade 0 (≥ 80%); grade 1 (66–80%); grade 2 (51–65%); grade 3 (≤ 50%).

Statistical analysis

Results are expressed as median and ranges. Statistical comparison between groups was performed with the Mann-Whitney U test for continuous and Fisher's exact test for discrete variables. All tests of significance were two-sided, and a p value of 0.05 or less was considered to be significant. The Kaplan-Meier method was used to estimate survival distributions, and the log-rank test was used for univariate analyses To examine relations between survival and selected demographic, donor-, transplant procedure-, and treatment-related variables univariate analysis based on Cox proportional hazards model was used. Results are expressed as hazard ratios with 95% confidence intervals (CI). To test wether potential predictors account for improved prognosis we adjusted the time period effect for explanatory variables with a p value of 0.15 or less in univariate analysis.

Results

The baseline characteristics of the two study populations are shown in table 1. There were more female patients during the early period (p = 0.0083). Recipients' age did not differ significantly. Median waiting time increased from 87 to 121 days (p = 0.027). Distribution of underlying diagnoses in the two periods was comparable, cystic fibrosis being the most frequent.

During the recent period, patients received lungs from older donors (p = 0.025). Causes of donor death and number of HLA matches were comparable during the two periods. Whereas overall distribution of cytomegalovirus serology was evenly distributed, significantly more seronegative patients received an organ from a seropositive donor during the recent period (p = 0.026).

Table 1

Baseline characteristics of the two study populations. Data are expressed as numbers or medians, with ranges shown in parenthesis.

	early period (n = 47)	recent period (n = 46)	p value
Sex ♀ / ♂	32 / 15	19 / 27	0.0083
Age yrs	39 (13–60)	39 (12–66)	0.66
Waiting time days	87 (1–292)	121 (1–891)	0.027
Diagnosis			0.38
Cystic fibrosis / bronchiectasis	12 / 5	17 / 0	
COPD / alpha 1-antitrypsin deficiency	5 / 3	6 / 6	
PPH / thromboembolic pulmonary hypertension	4 / 3	3 / 2	
Idiopathic pulmonary fibrosis	7	4	
Lymphangioleiomyomatosis	4	3	
Sarcoidosis / Langerhans-cell granulomatosis	2 / 0	1 / 2	
Various*	2	2	
Donor age yrs	33 (14–59)	39 (11–60)	0.025
Traumatic brain injury	27	24	0.38
HLA matches			0.14
A locus	16	17	
B locus	4	6	
DR locus	14	9	
Cytomegalovirus serology donor – recipient			0.076
Negative – negative	21	18	
Negative or positive – positive	18	11	
Positive – negative	8	17	(0.026)

* Giant cell interstitial pneumonitis, drug-induced bronchiolitis obliterans (early period); adult respiratory distress syndrome, pulmonary fibrosis after bone marrow transplantation (recent period).

Table 2

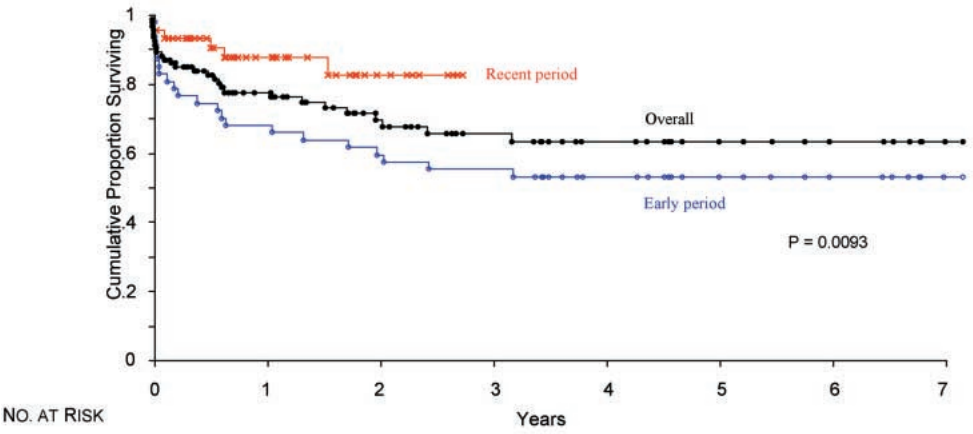
Transplant procedure-related data. Data are expressed as numbers or medians, with ranges shown in parenthesis.

	early period (n = 47)	recent period (n = 46)	p value
Single / bilateral lung transplantation	19 / 28	2 / 44	<0.0001
Total cold ischaemia time min*	328 (180–515)	273 (132–425)	0.012
Operation time min*	400 (295–550)	325 (140–515)	<0.0001
Anaesthesia time min*	598 (480–780)	480 (220–780)	<0.0001
Necessity for cardiopulmonary bypass	10	5	0.14
Transfusion requirements no. of blood units	2 (0–40)	2 (0–21)	0.94
Mechanical ventilation days	2 (1–218)	1 (1–32)	<0.0001
Intensive care stay days	8.5 (1–218)	6 (3–42)	0.061
Hospital stay days	30 (1–280)	30 (6–179)	0.90
Surgical complications			
Haemothorax	7	3	0.17
Sternal dehiscence / sternal infection	3	2	0.51
Bronchial anastomotic complications	0	0	NA
Severe native lung complications	9	0	NA
Severe overinflation necessitating LVRS	4	0	
Invasive infection (2× Aspergillus fumigatus, 1× Mycobacterium tuberculosis)	3	0	
Pneumothorax necessitating VATS	2	0	

* With respect to bilateral lung transplantation

Figure 1

Kaplan-Meyer estimates of survival after lung transplantation. The difference between the early and the recent period was calculated by the log-rank test.



Due to our experience of a high complication rate in the remaining native lung (45%; table 2), only two single lung transplants were performed during the recent period (p <0.0001). Total cold ischaemia, operation and anaesthesia time and duration of mechanical ventilation were significantly shorter during the recent period. Intensive care and hospital stay did not differ significantly. Surgical complications were rare and evenly distributed. Notably, no patient died of technical failure, and there were no bronchial anastomotic complications at overall 166 airway anastomoses.

Overall survival at two and five years was 70% and 63%, respectively (fig. 1). Follow-up was obviously longer for patients operated during the early period (table 3). Survival at two years was significantly better in the recent period (82% vs. 60%; p = 0.0093). While the first 19 patients received regular cyclosporine A, all subsequent patients were treated with neoral (p <0.0001). However, all patients on cyclosporine A later were switched to neoral. Thirty-four patients received mycophenolate mofetil during the second study period compared to none in the first period (p <0.0001). However, thirteen patients initially treated with azathioprine were switched to mycophenolate mofetil due to recurrent acute rejection episodes or BOS. Use of photopheresis for the two indications mentioned above was equally distributed between the two periods.

The total number of acute rejection episodes per patient at risk decreased from 1.70 to 0.69 (p = 0.017). Significantly more patients suffered from two or more acute rejection episodes during the early period (p = 0.0019). The Kaplan-Meier estimates of the cumulative incidence of BOS tended to be lower in the recent group (p = 0.097), and significantly fewer patients died due to this disorder after 1997 (p = 0.021; fig. 2). Overall cumulative incidence of BOS was 34% at five years.

Table 3

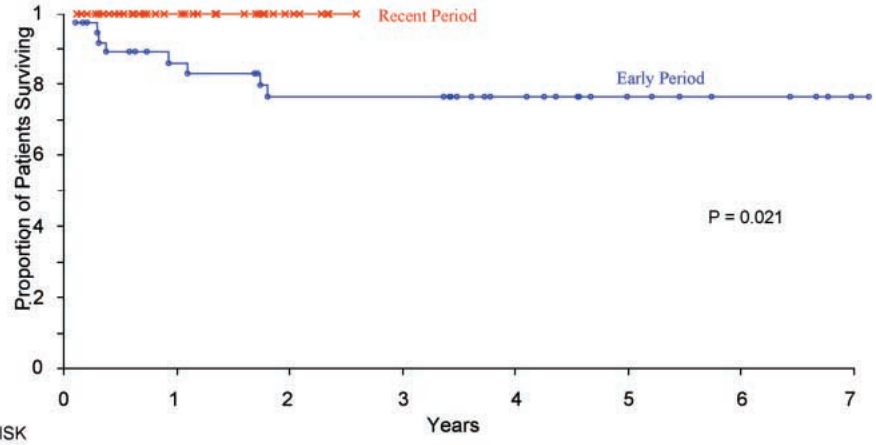
Treatment and outcome. Data are expressed as numbers or medians, with ranges shown in parenthesis.

	early period (n = 47)	recent period (n = 46)	p value
Follow-up (days)	1235 (1–2602)	646 (6–993)	0.004
Immunosuppression (no. of patients)			
Cyclosporine / neoral	18 / 29	0 / 46	<0.0001
Azathioprine / mycophenolate mofetil	46 / 0a	12 / 34	<0.0001
Conversion from azathioprine to Mycophenolate mofetil	10	3	0.038
Photopheresis	3	7	0.15
Acute rejection episodes per patient at risk[b]	1.70	0.69	0.017
Patients with ≥2 acute rejection episodes[b]	21	8	0.0019
BOS in patients at risk[c]	13	3	0.097
Grade 1	1	1	
Grade 2	4	1	
Grade 3	8	1	
Deaths due to bronchiolitis obliteransc	8	0	0.021
Ganciclovir prophylaxis / no. of patients at risk[d]	14	28	0.0006
Cytomegalovirus disease	7	4	0.13

[a] One patient received cyclophosphamide instead of azathioprine.
[b] Patients surviving at least 7 days (43 in the early period; 45 in the recent period); not related to follow-up time since 95% of acute rejection episodes occurred within the first 6 postoperative months.
[c] Patients surviving at least 60 days (38 in the early period; 43 in the recent period); the p-values were calculated by the log-rank test.
[d] Patients surviving at least 7 days and either donor and/or recipient seropositive for cytomegalovirus (22 in the early period; 28 in the recent period).

Figure 2

Kaplan-Meier estimates of the cumulative incidence of freedom from death due to bronchiolitis obliterans syndrome. The difference between the early and the recent period was calculated by the log-rank test.



NO. AT RISK

Early Period	38	28	23	23	16	8	5	1
Recent Period	43	24	7	0	0	0	0	0

While all patients at risk received ganciclovir prophylaxis during the second study period, only 14 of 22 patients did during the first time period (p = 0.0006). Due to the considerable number of patients receiving prophylaxis already during the first study period, the cumulative incidence of cytomegalovirus disease was comparable in the two periods. On an intention-to-treat basis, however, the cumulative incidence of cytomegalovirus disease was significantly lower in the patients receiving ganciclovir prophylaxis (12% vs. 75%; p <0.0001). Moreover, the patients on prophylaxis had a lower cumulative incidence of BOS (p = 0.025) and better survival (p = 0.0043; data not shown).

The most frequent causes of death were BOS followed by multiple organ failure without any specific aetiology, and invasive aspergillosis (table 4).

In the univariate analysis, the following parameters were not significantly associated with survival during the two periods (table 5): recipient age and sex, donor age, presence of a HLA match, transplantation type, total cold ischaemia time, operation time, anaesthesia time, duration of mechanical ventilation, intensive care stay, hospital stay, and immunosuppression with neoral. The need for cardiopulmonary bypass and number of transfusions required adversely influenced survival. Besides a transplantation date of 1997 or later, ganciclovir prophylaxis and immunosuppressive treatment with mycophenolate mofetil instead of azathioprine had a positive impact on survival.

Table 4

Causes of death.

	early period (n = 22)	recent period (n = 6)
Bronchiolitis obliterans syndrome	8	0
Multiple organ failure syndrome	4	3
Invasive aspergillosis	2	1
Hypoxic-ischaemic encephalopathy	2	0
Idiopathic hyperammonaemia	1	1
Miliary tuberculosis	0	1
Post-transplant lymphoproliferative disease	1	0
Posteroperative heart failure	1	0
Myocarditis of unknown aetiology	1	0
Encephalitis of unknown aetiology	1	0
Mesenteric infarction	1	0

Table 5

Univariate relative risk of dying for selected baseline values.

	Hazard ratio	95% CI	p value
Transplantation date 1997 or later	0.33	0.13–0.84	0.011
Recipient age, per additional 10 years	0.99	0.73–1.34	0.96
Recipient sex, female versus male	0.72	0.33–1.57	0.40
Donor age, per additional 10 years	0.90	0.67–1.20	0.46
At least one HLA match	0.58	0.27–1.25	0.15
Transplant type, bilateral versus single	0.73	0.33–1.63	0.45
Total cold ischaemia time, per additional 15 minutes	1.07	0.99–1.17	0.11
Operation time, per additional 15 minutes	1.05	0.97–1.14	0.21
Anaesthesia time, per additional 15 minutes	1.01	0.95–1.08	0.69
Necessity for cardiopulmonary bypass	3.26	1.43–7.45	0.011
Transfusion requirements, per blood unit	1.09	1.03–1.14	0.0041
Mechanical ventilation, per additional day	1.01	1.00–1.02	0.059
Intensive care stay, per additional day	1.01	1.00–1.02	0.09
Hospital stay, per additional week	1.01	0.94–1.09	0.81
Ganciclovir prophylaxis	0.28	0.09–0.94	0.049
Immunosuppression			
Neoral versus cyclosporine	0.66	0.30–1.48	0.32
Mycophenolate mofetil versus azathioprine	0.16	0.04–0.67	0.0014

Table 6

Time period effect adjusted for potential explanatory variables.

	Hazard ratio	95% CI
Transplantation date 1997 or later, not adjusted	0.33	0.13–0.84
Adjusted for:		
At least one HLA match	0.35	0.14–0.88
Total cold ischaemia time	0.39	0.14–0.93
Necessity for cardiopulmonary bypass	0.38	0.15–0.97
Transfusion requirements	0.31	0.11–0.84
Duration of mechanical ventilation	0.37	0.15–0.94
Intensive care stay	0.36	0.14–0.92
Ganciclovir prophylaxis	0.50	0.09–2.91
Immunosuppression with mycophenolate mofetil versus azathioprine	0.80	0.27–2.36
Ganciclovir prophylaxis and immunosuppression with mycophenolate mofetil versus azathioprine	1.24	0.14–11.39

In order to elucidate relevant factors contributing to the improved survival after lung transplantation since 1997, all parameters influencing survival at a p value of 0.15 or lower in the univariate model were entered one-by-one into a multivariate analysis together with the transplantation period. Adjustment for presence of at least one HLA match, total cold ischaemia time, necessity for cardiopulmonary bypass, transfusion requirements, duration of mechanical ventilation and in-

tensive care stay did not materially alter the reduced risk in the recent period (table 6). However, adjustment for ganciclovir prophylaxis and immunosuppression with mycophenolate mofetil attenuated the time period effect from 0.33 to 0.50 (95% CI, 0.09–2.91) and to 0.80 (95% CI, 0.27–2.36), respectively. With adjustment for both ganciclovir prophylaxis and immunosuppression with mycophenolate mofetil, the beneficial time period effect was completely abolished (hazard ratio 1.24; 95% CI, 0.14–11.39).

Analysing the beneficial effect of immunosuppression with mycophenolate mofetil on an intention-to-treat basis we found a significant reduction in number of acute rejection episodes per patient at risk from 1.53 in the patients receiving azathioprine to 0.62 in those treated with mycophenolate mofetil. Only two patients in the mycophenolate mofetil group experienced two or more acute rejection episodes compared with 12 in the azathioprine group ($p = 0.033$). The Kaplan-Meier estimates of the cumulative incidence of BOS and the occurrence of death due to this disorder alone tended to be lower in the mycophenolate mofetil group ($p = 0.27$ and $p = 0.097$, respectively; data not shown).

Discussion

The current study demonstrates improved survival after lung transplantation during recent years. The analysis of possible factors contributing to this success suggests that novel immunosuppressive therapy with mycophenolate mofetil instead of azathioprine and, to a lesser extent, antiviral prophylaxis with ganciclovir were most relevant. The beneficial effect of mycophenolate mofetil, as shown by other authors [23–25] and by our intention-to-treat analysis, might be due to a significant reduction in the number of acute rejection episodes per patient and in the number of patients with two or more acute rejection episodes. These are the most important known risk factors for development of BOS [7–11]. The beneficial effect of the decrease in acute rejection episodes is suggested by a trend towards a decrease in the cumulative incidence of the BOS and the significantly reduced cumulative incidence of death due to this disorder.

Antiviral prophylaxis with ganciclovir was the second important factor contributing to improved survival rates in the present series. The relatively small effect may be due to the fact that this treatment option was implemented very early in our programmeme [16]. Only the first eight patients did not receive prophylactic ganciclovir, and they experienced an unacceptably high rate of cytomegalovirus disease of 75%. Besides mortality due to cytomegalovirus disease itself, fungal superinfection is a major threat to these patients [26] and contributed directly or indirectly to fatal outcome in three of our patients. Moreover, cytomegalovirus infection and disease may propagate development of BOS [27]. Hence, we [16] and others [28, 29] have shown that ganciclovir prophylaxis significantly reduces the cumulative incidence of BOS. The present series further corroborates these data by an intention-to-treat analysis showing a decreased occurrence of BOS and improved survival among patients receiving ganciclovir.

Notwithstanding, various other factors related to improved experience reflected by reduced ischaemia, operation and anaesthesia time, and shorter duration of postoperative mechanical ventilation may also have contributed to lesser graft injury and more rapid recovery of patients. Additionally, the evolution of the program as a whole, with an increase in awareness and know-how may have facilitated a multitude of beneficial minor clinical decisions in a fashion not measurable in this study.

Overall survival in the present series compares favourably with the data from the registry of the International Society for Heart and Lung Transplantation [3]. With respect to different time periods, the registry also documents an improvement in survival at two years from 57% to 68% from the era 1988–1991 to the era 1996–1999.

Overall cumulative incidence of BOS of 34% at five years was lower in comparison to 63% to 75% reported in other series [7–9, 30, 31]. One of the many reasons might be our strict post-transplant surveillance with monthly surveillance biopsies during the first six months. Significant acute rejection episodes (grade A2 or higher) can be found in about 20% to 30% of completely asymptomatic, functionally stable lung transplant recipients. Hence, we believe that early detection and treatment of these asymptomatic rejection episodes might reduce the subsequent occurrence of BOS. However, the present data cannot prove this hypothesis.

A limitation of this study might be the fact that the transplant volume of our programme is in a medium range, and therefore the number of patients was limited. However, our annual volume of about 15 procedures corresponds well with general practice. In the United States only 35 out of almost 90 programmes performed more than 10 transplantations in 1997 [1]. Moreover, the fact that the same team cared for the patients throughout the whole study period guaranteed that besides the above mentioned factors, criteria for selection of candidates and donors, operative procedure and postoperative regimen were only minimally modified throughout the whole study period. All transplantations were performed by a single surgeon, and no technical failures or bronchial anastomotic complications occurred. This high consistency,

however, might be achieved to a lesser extent in collaborative studies. Technical problems such as bronchial anastomotic complications might obscure contributing factors.

In conclusion, the present data suggest that improved immunosuppression with mycophenolate mofetil and prophylaxis with ganciclovir in addition to careful postoperative surveillance and surgical expertise can lead to improved results after lung transplantation.

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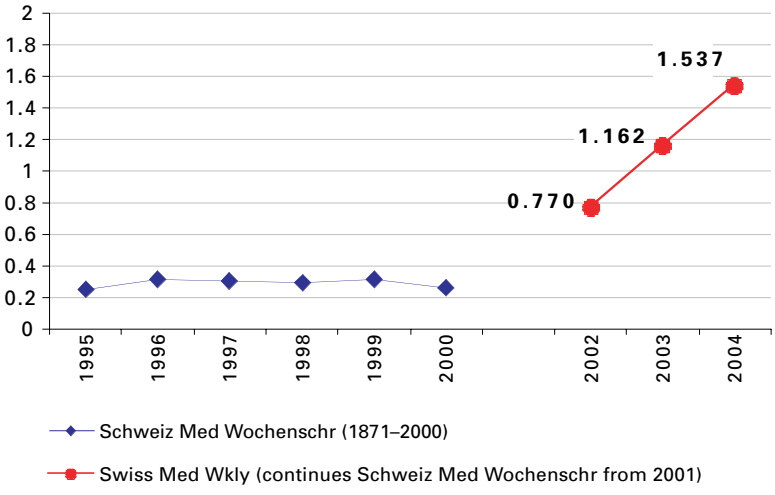

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